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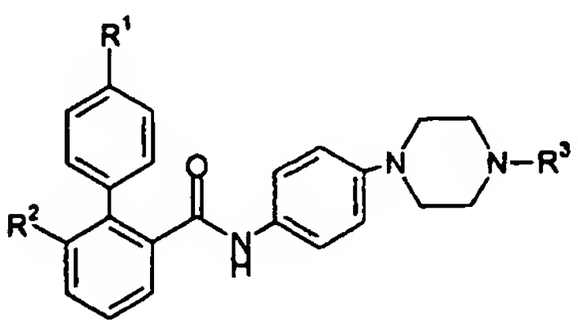
(54) Title: THERAPEUTIC BENZAMIDE DERIVATIVES



(I)

(57) Abstract: Therapeutically active benzamide derivatives of formula (I), processes for the preparation thereof, the use thereof in therapy, particularly in the treatment or prophylaxis of conditions ameliorated by an apoB-100 and/or MTP inhibitor, and pharmaceutically compositions for use in such therapy.

Therapeutic Benzamide Derivatives

The invention relates to therapeutic benzamide derivatives, their use in inhibiting hepatic production of apoprotein B-100 (apoB-100) and intestinal production of chylomicrons or apoprotein B-48 (apoB-48) and MTP, and intermediates useful in the production of such derivatives.

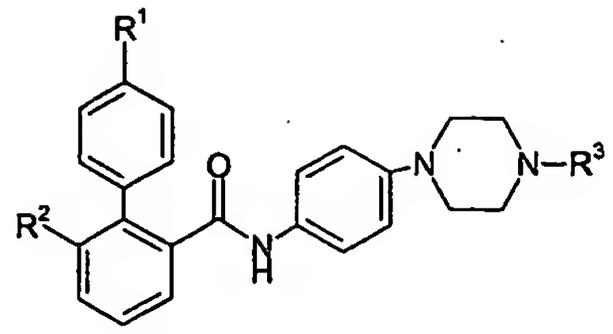
ApoB-100 is the main protein component of low density lipoprotein-cholesterol (LDL-c). High LDL-c plasmatic levels are a major risk factor for atherosclerosis and coronary artery diseases. ApoB-48 is the main protein component of chylomicrons.

The microsomal triglyceride transfer protein (MTP) catalyses the transfer of triglycerides, cholesteryl esters and phosphatidylcholine between small unilamellar vesicles. MTP is expressed in liver and intestine, both organs which produce lipoproteins. MTP is able to lipidate neosynthesized apoB-100 within the liver, and neosynthesized apoB-48 within the intestine, therefore leading to the production of triglyceride-rich lipoparticles such as VLDL and chylomicrons respectively. Thus, MTP inhibitors have the potential to decrease LDL-c and triglyceride plasmatic levels, and also intestinal lipid absorption. MTP inhibitors may be used in the treatment of non-insulin dependent diabetes mellitus, coronary heart disease, pancreatitis, mixed dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipemia, post-prandial hyperlipemia, atherosclerosis and obesity.

Compounds having apoB-100 and MTP inhibition properties have been described in WO96/40640. International Patent Application no. PCT/EP99/09320 describes therapeutic benzamide compounds for the treatment of conditions resulting from elevated circulating levels of apoB-100.

Surprisingly, it has been found that compounds according to the present invention, generically disclosed in PCT/EP99/09320, and having a specific substitution pattern, exhibit improved properties over those compounds specifically disclosed in PCT/EP99/09320.

Thus, the present invention provides a compound of formula (I);



(I)

wherein

R^1 represents isopropyl or trifluoromethyl,

R^2 represents isopropyl, chloro, fluoro or trifluoromethyl,

R^3 represents C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{1-4}alkylsulfonyl, C_{1-4}acyl or $-CH_2-R^4$;

R^4 represents:

(i) phenyl, optionally substituted by cyano, fluoro or an optionally substituted 5-membered heteroaromatic group, where optional substitution is effected by C_{1-4}alkyl or C_{1-3}perfluoroalkyl,

(ii) a 5- or 6- membered heteroaromatic group, optionally substituted by halogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy or C_{3-7}cycloalkyl,

(iii) C_{3-7}cycloalkyl,

(iv) cyano,

(v) hydroxycarbonyl, C_{1-4}alkoxycarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl, C_{1-4}dialkylaminocarbonyl,

(vi) C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or

(vii) trifluoromethylC_{1-4}alkyl;

or a physiologically acceptable salt, solvate or derivative thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic and inorganic acids for example, citrates, hydrochlorides, hydrobromides, or sulphates. Particularly preferred salts are citrates or hydrochloride salts.
The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their physiologically acceptable salts together with physiologically acceptable solvates.

Referring to the general formula (I), alkyl, alkylene and alkoxy include both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl and ethyl groups, examples of alkylene groups include methylene and ethylene groups, whilst examples of alkoxy groups include methoxy and ethoxy groups.

Referring to the general formula (I), reference to alkenyl includes both straight and branched chain saturated hydrocarbon groups containing one double bond, e.g. 3-methyl-but-2-ene and propen-2-yl.

Referring to the general formula (I), reference to a heteroaromatic group, unless otherwise defined, means any single aromatic ring containing at least one ring heteroatom independently selected from O, N and S.

Referring to the general formula (I), reference to a halogen group includes fluoro, chloro, bromo and iodo groups.

R^1 is preferably isopropyl.

R^2 is suitably isopropyl or trifluoromethyl. R^2 is preferably isopropyl.

R^4 suitably represents:

i) phenyl, optionally substituted by cyano, fluoro or an optionally substituted 5-membered heteroaromatic group, e.g. 3-methyl-[1,2,4]oxadiazol-5-yl,

ii) a 5- or 6- membered heteroaromatic group, e.g. pyrrolyl, furanyl, pyridyl, thienyl, thiazolyl, pyrazolyl or imidazolyl, optionally substituted by halogen, e.g. fluoro or bromo, cyano or C_{1-4}alkyl, e.g. methyl,

iii) C_{3-7}cycloalkyl, e.g. cyclopropyl

iv) cyano,

v) C_{1-4}alkoxycarbonyl, e.g. ethoxycarbonyl, hydroxycarbonyl, aminocarbonyl,

vi) C_{1-4}alkoxymethyl, e.g. methoxymethyl, hydroxyC_{1-4}alkyl, e.g. hydroxymethyl, or

vii) trifluoromethylC_{1-4}alkyl, e.g. 1,1,1-trifluoroethyl;

Where R^4 represents an optionally substituted 5- or 6- membered heteroaromatic group, suitable optional substituents are selected from halogen, e.g. fluoro or bromo, cyano or C_{1-4}alkyl, e.g. methyl.

Where R^4 represents C_{1-4}alkoxymethyl, this is suitably methoxymethyl.

R^3 is suitably selected from C_{1-4}alkyl e.g. methyl , ethyl, isopropyl, propyl or isobutyl, C_{2-6}alkenyl e.g. prop-2-enyl, acetyl, methylsulfonyl or $-CH_2-R^4$ wherein R^4 is suitably aminocarbonyl, cyano, ethoxycarbonyl, hydroxycarbonyl, C_{1-4}alkoxymethyl e.g. methoxymethyl, trifluoromethylC_{1-4}alkyl, e.g. 1,1,1-trifluoroethyl, C_{3-7}cycloalkyl e.g. cyclopropyl, phenyl substituted by 3-fluoro, 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or a 5- or 6- membered heteroaromatic group, e.g. pyrrolyl, furanyl, pyridyl, thienyl, thiazolyl, pyrazolyl or imidazolyl, optionally substituted by bromo, methyl or cyano.

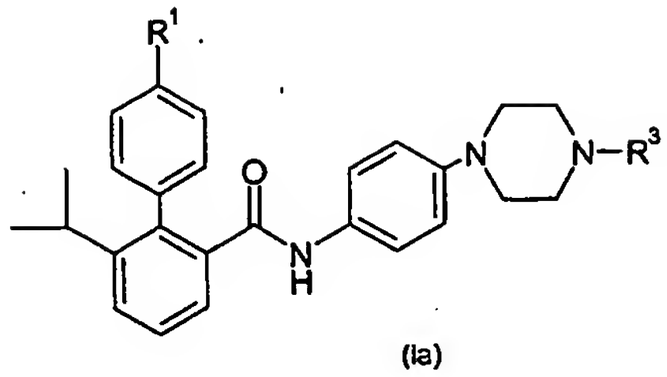
R^3 is more suitably methyl, propyl, isopropyl, propen-2-yl, methoxyethyl, phenylmethyl substituted by 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or an optionally substituted pyrrolylmethyl, thienylmethyl or furanylmethyl group, where optional substitution is effected by methyl or cyano.

Alternatively, R^3 is more suitably methyl, propyl, isopropyl, isobutyl, propen-2-yl, methoxymethyl, hydroxyethyl, phenylmethyl substituted by 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or an optionally substituted pyrrolylmethyl, thienylmethyl or furanylmethyl group, where optional substitution is effected by methyl or cyano.

R^3 is preferably propyl, propen-2-yl, or phenylmethyl substituted by 3-cyano. Alternatively, R^3 is preferably propyl, isobutyl, propen-2-yl, furanylmethyl substituted by 5-cyano, or phenylmethyl substituted by 3-cyano. Most preferably, R^3 is propyl or propen-2-yl.

Particularly preferred compounds of the invention include those in which each variable in formula (I) is selected from the preferred groups for each variable. Even more preferable compounds of the invention include those where each variable in formula (I) is selected from the more preferred or most preferred groups for each variable.

A suitable sub-group of a compound of formula (I) is represented by formula (Ia)



(Ia)

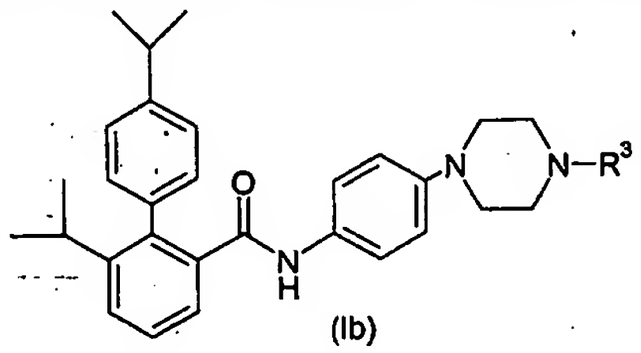
wherein

R^1 represents isopropyl or trifluoromethyl,

R^3 represents C_{1-4}alkyl, C_{2-6}alkenyl, acetyl, methylsulfonyl or $-CH_2-R^4$;

R^4 represents aminocarbonyl, cyano, ethoxycarbonyl, hydroxycarbonyl, C_{1-4}alkoxymethyl, trifluoromethylC_{1-4}alkyl, C_{3-7}cycloalkyl, phenyl substituted by 3-fluoro, 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or a 5- or 6- membered heteroaromatic group, optionally substituted by bromo, methyl or cyano.

A further suitable sub-group of a compound of formula (I) is represented by formula (Ib)



(Ib)

wherein

R^3 represents C_{1-4}alkyl ,C_{2-6}alkenyl or $-CH_2-R^4$; and

R^4 represents phenyl substituted by 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or a 5- membered heteroaromatic goup selected from pyrrolyl, thienyl, furanyl, thiazolyl and pyrazolyl, optionally substituted by halogen or methyl.

Alternatively, R^4 represents phenyl substituted by 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or a 5- membered heteroaromatic goup selected from pyrrolyl, thienyl, furanyl, thiazolyl and pyrazolyl, optionally substituted by halogen, methyl or

cyano;

or a physiologically acceptable salt, solvate or derivative thereof.

It will be clear that references herein to a compound of formula (I) apply equally to a compound of formula (Ia) or (Ib).

Suitable compounds according to the invention include:
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-carbamoylmethyl-piperazin-1-yl)-phenyl] amide;
6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-carbamoylmethyl-piperazin-1-yl)-phenyl] amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl)-phenyl]-amide;
6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl)-piperazin-1-yl)-phenyl]-amide;
6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((thien-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((furan-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((thiazol-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((5-bromo-furan-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((5-bromo-thien-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((2-methyl-thiazol-4-yl)methyl)-piperazin-1-yl)phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid {4-[4-(5-cyano-furan-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-allyl-piperazin-1-yl)-phenyl]-amide
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((pyrazol-3-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((thien-3-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((3-methyl-pyrrol-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-propyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(cyano-methyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((pyridin-2-yl)-methyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((pyridin-3-yl)-methyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((pyridin-4-yl)-methyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-fluorobenzyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
6-fluoro-4'-isopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
6-fluoro-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
6-chloro-4'-isopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
4'-isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-isopropyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((5-cyano-furan-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;

4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((1-methyl-pyrrol-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((ethoxycarbonyl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((hydroxycarbonyl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(cyclohexyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((cyclopropyl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-methyl-but-2-enyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(acetyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(methanesulfonyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(propen-2-yl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(2-methoxyethyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3,3,3-trifluoro-propyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(2-hydroxyethyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((2-methyl)propyl)-piperazin-1-yl)phenyl]-amide;
6-isopropyl-4'-trifluoromethyl--biphenyl-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide;
6-isopropyl-4'-trifluoromethyl--biphenyl-2-carboxylic acid [4-(4-propyl-piperazin-1-yl)-phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-ethyl-piperazin-1-yl)-phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-isopropyl-piperazin-1-yl)-phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid {4-[4-(3,3,3-trifluoro-propyl)-piperazin-1-yl]-phenyl}-amide;

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-allyl-piperazin-1-yl)-phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl -biphenyl-2-carboxylic acid {4-[4-(5-cyano-furan-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide;
6-Isopropyl-4'-trifluoromethyl -biphenyl -2-carboxylic acid {4-[4-(5-cyano-1H-pyrrol-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide;
6-Isopropyl-4'-trifluoromethyl -biphenyl -2-carboxylic acid {4-[4-(4-cyano-1H-pyrrol-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide;
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(5-cyano-1H-pyrrol-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide;
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(4-cyano-1H-pyrrol-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide;
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-ethyl-piperazin-1-yl)-phenyl]-amide;
or a physiologically acceptable salt, solvate or derivative thereof.

Preferred compounds of the invention include:
4'-isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid {4-[4-(5-cyano-furan-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((thien-3-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((furan-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;

4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((5-cyano-furan-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-propyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-isopropyl-piperazin-1-yl)-phenyl]-amide;
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-isobutyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(propen-2-yl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(2-methoxyethyl)-piperazin-1-yl)-phenyl]-amide;
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(2-hydroxyethyl)-piperazin-1-yl]-phenyl}-amide;
or a physiologically acceptable salt, solvate or derivative thereof.

The term "physiologically functional derivative" as used herein refers to any physiologically acceptable derivative of a compound of the present invention, for example, an ester or amide, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice, which is incorporated herein by reference.

The compounds of the invention are inhibitors of hepatic production of apoB-100 and MTP and are thus of use in the treatment of conditions ameliorated by an apoB-100 and / or MTP inhibitor.

The ability of the compounds of this invention to inhibit human MTP activity is measured by an in vitro assay where MTP transfers 3H-triolein between phosphatidylcholine liposomes. The specificity of the compounds of the invention is established by comparing the effects on apoB-100 and apoprotein A-1 production. A specificity of at least 100 is preferred.

The in vivo profile of the compounds is determined by acute oral administration of the compounds of the invention to DBA/2 mice and Wistar rats. Potency of the active compounds is evaluated by measuring plasmatic lipids (total cholesterol, triglyceride, LDL cholesterol and HDL cholesterol) and apoproteins (apoB-100, apoB-48 and apoA-1).

The compounds of the invention are potent and specific inhibitors of hepatic production of apoB-100 and MTP, which furthermore exhibit good oral bioavailability and duration of action.

Furthermore, the compounds of the present invention exhibit significant oral activity compared with compounds of the prior art. They also possess favourable pharmacokinetic profiles compared with compounds of the prior art.

Compounds of the invention are of use in the treatment of atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), coronary heart diseases and obesity.

Compounds of the invention are also useful in lowering serum lipid levels, cholesterol and/or triglycerides, and are of use in the treatment of hyperlipemia, hyperlipidemia, post-prandial hyperlipemia, mixed dislipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia.

The invention therefore provides a compound of formula (I) or a physiologically acceptable salt, solvate or derivative thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a physiologically acceptable salt, solvate or derivative thereof in the preparation of a medicament for use in the treatment of conditions ameliorated by an apoB-100 and / or MTP inhibitor.

In an alternative or further aspect, there is provided a method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound of formula (I) or a physiologically acceptable salt, solvate or derivative

thereof in particular in the treatment of conditions ameliorated by an apoB-100 and / or MTP inhibitor.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

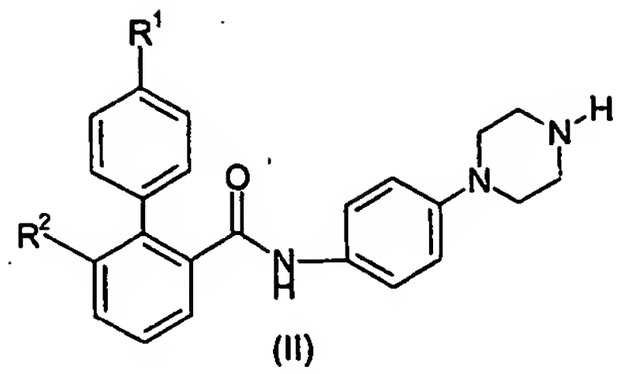
Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a physiologically acceptable salt, solvate or derivative thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, transdermal, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The compounds of formula (I) may, if desired, be administered with one or more therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the compounds of formula (I) may be administered in combination with an HMG CoA reductase inhibitor.

A compound of formula (I), or a physiologically acceptable salt, solvate or derivative thereof, may be prepared by the general methods outlined hereafter. In the following description, the groups R^1, R^2 and R^3 are as previously defined for compounds of formula (I), unless specified otherwise.

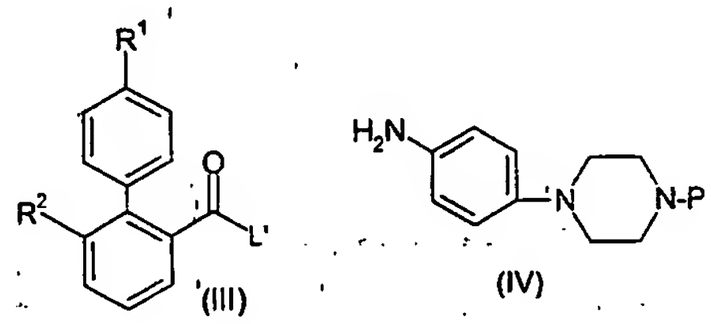
According to a general process (A), a compound of formula (I) may be prepared by reacting a compound of formula (II) with a compound of formula R^3-L



(II)

where L represents a suitable halide leaving group, e.g. chloride, under standard displacement conditions or L may additonally represent a hydroxy group, the reaction being effected under standard acid and amine coupling conditions.

A compound of formula (II) may be prepared by reaction of a compound of formula (III) with a compound of formula (IV)

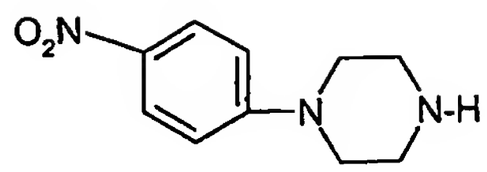


(III) (IV)

where L' is a suitable leaving group, such as chloride, or an OH group and P is a suitable amine protecting group, e.g. tert-butoxycarbonyl (Boc), under standard coupling conditions for an acid and amine coupling, followed by deprotection of the protecting group under suitable conditions, e.g. acidic removal of a Boc group.

An intermediate of formula (III), wherein L' is OH, R^1 is isopropyl or trifluoromethyl and R^2 is chloro, fluoro, isopropyl or trifluoromethyl, is new and represents a further aspect of the present invention. An intermediate of formula (III) wherein L' is OH, R^1 is isopropyl or trifluoromethyl and R^2 is isopropyl or trifluoromethyl is preferred. An intermediate of formula (III) where L' is OH and R^1=R^2=isopropyl is a particularly preferred further aspect of the present invention.

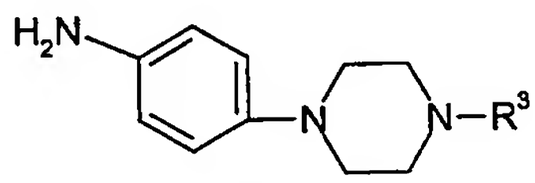
A compound of formula (IV) may be prepared by the two step reaction of a compound of formula (V)



(V)

comprising incorporation of the protecting group P using standard methodology followed by reduction of the nitro group, e.g. under hydrogenation conditions.

According to a second method (B), compounds of formula (I) may be prepared by reaction of compounds of formula (III) and compounds of formula (VI)

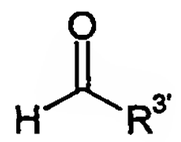


(VI)

where L is defined above, under standard coupling conditions.

Compounds of formula (VI) may be prepared by reaction of a compound of formula (V) with a compound of formula R^3-L, where L is defined above, followed by reduction of the nitro group under hydrogenation or reductive tin chloride conditions.

According to a third general process (C), a compound of formula (I), where there is an alkylene link to the piperazine group, may be prepared by reacting a compound of formula (II) with a compound of formula (VII)



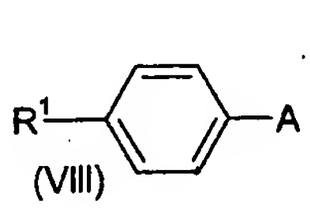
(VII)

where $R^{3'}$ represents R^3 minus a methylene group, under standard reductive amination conditions, e.g. using sodium triacetoxyborohydride in a solvent such as dichloroethane.

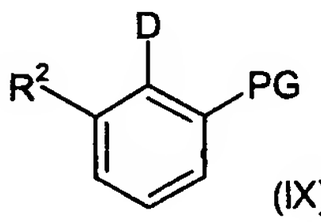
According to a fourth process (D), a compound of formula (I) may be prepared from a different compound of formula (I), using standard techniques well known in the art. For

example, compounds of formula (I) where R^3 comprises a group containing an amide group may be prepared from the compound of formula (I) where the corresponding position comprises a carboxylic acid group, which in turn may be prepared from the compound of formula (I) where the corresponding position comprises a carboxylic ester group. Well known methods in the art may be employed to facilitate the transformation of an ester to an acid ahd then to an amide.

A compound of formula (III), where L' is a hydroxy group, may be prepared firstly by coupling a boronic acid with a suitable leaving group, represented by a compound of formula (VIII) and a compound of formula (IX)



(VIII)



(IX)

where PG represents a protected carboxylic acid and A and D represent either the boronic acid or the suitable leaving group, such as triflate or bromide, followed by deprotection of the protecting group under standard conditions, such as base removal of an ester group. Where L represents a halide leaving group, the carboxylic acid product can be treated with a suitable reagent, such as thionyl chloride, to give the corresponding chloride leaving group.

Where R^3 is a phenylmethyl, substituted by an optionally substituted 5-membered heteroaromatic group, the heteroaromatic group may be introduced by any well known methods in the art. For instance, where the substituent is a methyl substituted oxadiazole, this may be formed by treatment of a suitable benzamide derivative with a suitable reagent, such as dimethylacetamide dimethylacetal at elevated temperature, followed by cyclisation of the intermediate compound with hydroxylamine.

The various general methods described above may be useful for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

Compounds of formula R^3-L, (V), (VII), (VIII) and (IX) are known or may be prepared by standard methods well known in the art and/or herein described.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compound of formula (I) using conventional methods.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the enantiomeric mixture of a compound of general formula (I). The resulting mixture of isomeric salts may be separated, for example, by fractional crystallisation into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

The invention is further illustrated by the following intermediates and examples. All temperatures are in degrees centigrade.

Abbreviations:

AcOEt-Ethyl acetate

BuLi – butyl lithium

BINAP-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

CH_2Cl_2 – dichloromethane

CH_3CN – acetonitrile

DMSO - dimethylsulfoxide

EDCI-1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOH- Ethanol
Et_3N- Triethylamine
Et_2O – diethyl ether
HOBt-1-Hydroxybenzotriazole
LiCl – lithium chloride
MS - LCMS mass spectrography
MeOH - Methanol
$NaHCO_3$ – sodium hydrogencarbonate
Na_2CO_3 – sodium carbonate
$NiCl_2(dppf)$ – nickel 1,1- bis(diphenylphosphino)ferrocene dichloride
Na_2SO_4 – sodium sulphate
$Pd(PPh_3)_4$ – tetrakis(triphenylphosphine)palladium(0)
$SnCl_2.2H_2O$ – tin(II) chloride dihydrate
THF- Tetrahydrofuran

Intermediate 1

4'-6-Diisopropyl-biphenyl-2-carboxylic acid methyl ester

To a stirred solution of 3-isopropyl-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (2.3 g) in toluene (15 mL) was added LiCl (0.88 g) and $Pd(PPh_3)_4$ (0.4 g). After 10 minutes at room temperature, a 2M solution of Na_2CO_3 (7 mL) was added followed by 4-isopropylphenyl boronic acid (1.43 g) in EtOH (10 mL). The resulting mixture was heated under reflux during 6 hours and then cooled to room temperature. After decantation, the organic phase was diluted , washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as an oil (2.1 g).
GC/MS : m/z 296 (M+)

Similarly prepared were :

Intermediate 2

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester as an oil which crystallised (2.25 g),
GC/MS : m/z 322 (M+)
from 3-isopropyl-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (2.3 g) and 4-trifluoromethylphenyl boronic acid (1.59 g).

Intermediate 3

6-Fluoro-4'-isopropyl-biphenyl-2-carboxylic acid methyl ester as an oil (1.7 g),

GC/MS : m/z 272 (M+)

from 3-fluoro-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (2.08 g) and 4-isopropylphenyl boronic acid (1.27 g).

Intermediate 4

6-Fluoro-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester as an oil (1.9 g),

GC/MS : m/z 298 (M+)

from 3-fluoro-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (2.08 g) and 4-trifluoromethylphenyl boronic acid (1.48 g).

Intermediate 5

6-Chloro-4'-isopropyl-biphenyl-2-carboxylic acid methyl ester as an dark oil (3 g),

GC/MS : m/z 288 (M+)

from 3-chloro-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (3.5 g) and 4-isopropylphenyl boronic acid (2.28 g).

Intermediate 6

4'-Isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester

To a mixture of $NiCl_2$(dppf) (0.5 g) in dioxane (30 mL) was added dropwise BuLi (solution 2M in cyclohexane, 1.5 mL) and the mixture was stirred at room temperature during 10 minutes. Then were added 4-isopropylphenyl boronic acid (1.43 g), K_3PO_4 (4.65 g) and 2-chloro-3-trifluoromethyl-benzoic acid methyl ester (1.7 g) and the mixture was heated under reflux overnight. The catalyst was filtered off and the filtrate concentrated under reduced pressure. The residue was treated with water, extracted with diethyl ether. The organic phase was washed with water, dried over Na_2SO_4 and concentrated. After purification by flash chromatography eluting with cyclohexane/AcOEt (92/8), the title compound was obtained as an oil (0.37 g).

GC/MS : m/z 322 (M+).

Intermediate 7

4'-6-Diisopropyl-biphenyl-2-carboxylic acid

To a stirred solution of 4'-6-diisopropyl-biphenyl-2-carboxylic acid methyl ester (2.07 g) in ethanol (10 mL) was added a 1N solution of NaOH (21 mL) and the mixture was heated under reflux overnight. After concentration under reduced pressure, the residue was taken in water and the aquous phase was extracted with diethyl ether and then acidified with a 1N solution of HCl. The aqueous phase was extracted with diethyl ether and the resulting organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. After crystallization from $MeOH/H_2O$, the title compound was obtained as white crystals (1.6 g).

m.p. :123-125°C.

Similarly prepared were:

Intermediate 8

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid as a white solid (1.5 g),

m.p. :178-180°C

from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester (2.25 g).

Intermediate 9

6-Fluoro-4'-isopropyl-biphenyl-2-carboxylic acid as a white solid (1.6 g),

m.p. :125-127°C

from 6-fluoro-4'-isopropyl-biphenyl-2-carboxylic acid methyl ester (1.7 g).

Intermediate 10

6-Fluoro-4'-trifluoromethyl-biphenyl-2-carboxylic acid as a white solid (1.5 g),

m.p. :185-187°C

from 6-fluoro-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester (1.9 g).

Intermediate 11

6-Chloro-4'-isopropyl-biphenyl-2-carboxylic acid as a white solid (2.3 g),

m.p. :106-108°C

from 6-chloro-4'-isopropyl-biphenyl-2-carboxylic acid methyl ester (3 g).

Intermediate 12

4'-Isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid as a white solid (0.3 g),

m.p. :111-113°C

from 4'-isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester (0.37 g).

Intermediate 13

4-{4-[(4',6-Diisopropyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester

To a stirred solution of 4-(4-amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (14 g), 4',6-diisopropyl-biphenyl-2-carboxylic acid (14.25 g), HOBt (7.5 g), and Et_3N (7.8 mL) in CH_2Cl_2 (200 mL) was added EDCI (10.6 g) and the mixture was stirred at room temperature for 16 hours. The organic solution was then washed with water, with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After filtration and evaporation of the filtrate, the residue was purified by crystallization from diisopropyl ether to give the title compound (27 g) as a beige powder.

m.p. : 158-160°C.

Similarly prepared was :

Intermediate 14

4-{4-[(6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester as a powder (1.25 g),

m.p. : 100°C

from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (1 g) and 4-(4-amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (0.9 g).

Intermediate 15

4',6-Diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide

To a solution of 4-{4-[(4',6-diisopropyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (27 g) in CH_2Cl_2 (500 mL) was added trifluoroacetic acid (15.4 mL) and the solution was stirred at room temperature for 16 hours. The mixture was then evaporated under reduced pressure and the residue was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was then washed with water, dried over Na_2SO_4, filtered and evaporated to dryness. The solid obtained was recrystallized from CH_3CN to give the title compound (22 g) as white crystals.

m.p.: 178-180°C.

Similarly prepared was :

Intermediate 16

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide

as a white powder (1 g),

m.p. : 203-205°C

from 4-{4-[(6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (1.25 g).

Intermediate 17

1-(3-Cyano-benzyl)-4-(4-nitro-phenyl)-piperazine

To a stirred solution of 1-(4-nitro-phenyl)-piperazine (35.9 g) and potassium carbonate (71.6 g) in acetone (500 mL) was added dropwise 3-cyano-benzyl bromide (34 g) at room temperature and the mixture was heated under reflux. After 4 hours, the salts were removed by filtration, washed with acetone and the filtrate was evaporated to dryness. The residue was taken in CH_2Cl_2 and the solution was washed with water, dried over Na_2SO_4, filtered and evaporated. The oily residue was crystallized from AcOEt/diisopropyl ether to give the title compound (52 g) as orange crystals.

m.p. : 120-122°C.

Intermediate 18

4-[4-(3-Cyano-benzyl)-piperazin-1-yl]-phenylamine

To a stirred solution of 1-(3-cyano-benzyl)-4-(4-nitro-phenyl)-piperazine (52 g) in EtOH (1.2 L) and THF (300 mL) was added portionwise $SnCl_2.2H_2O$ (145.6 g) at room temperature and the mixture was heated at 55°C for 16 hours. After evaporation of the solvents, the residue was taken in water, basified with NaOH at pH 14 and extracted with CH_2Cl_2. The organic layer was then washed with water, dried over Na_2SO_4, filtered and evaporated. The residue was crystallized from diisopropyl ether to give the title compound (40.5 g) as pale yellow crystals.

m.p. : 99-101°C.

Intermediate 19

4-(4-Nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 1-(4-nitro-phenyl)-piperazine (15.5 g) in CH_2Cl_2 (250 mL) was added Et_3N (8.3 g). The solution was cooled to 0°C and di-tert-butyl dicarbonate (17.1 g) was added portionwise. After 16 hours at room temperature, the solution was washed with water, with a saturated solution of $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure and the resulting solid

was recrystallized from MeOH to give the title compound (21.5 g) as pale yellow crystals.
m.p: 149-151°C.

Intermediate 20
4-(4-Amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester
A solution of 4-(4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (21.4 g) in EtOH (250 mL) containing Pd/C 10% (0.5 g) was hydrogenated at room temperature. After 16 hours, the catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The oily residue was then crystallized from cyclohexane to give the title compound (17.8 g) as pink crystals.
m.p: 95-96°C.

Example 1
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl)-phenyl]-amide
To a solution of 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) in dichloromethane (20 mL) was added 1H-pyrrole-2-carboxaldehyde (104 mg) and acetic acid (66 mg). The solution was cooled at O°C and sodium triacetoxy borohydride (255 mg) was added portionwise and the mixture was stirred at room temperature for 16 hours. The solution was then washed with a saturated solution of $NaHCO_3$, with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (95/5) and crystallized from pentane to give the title compound (310 mg) as white crystals.
m.p. : 158-160°C
mass spec m/z : 521 (M+1)..

Similarly prepared were :
Example 2
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl)-phenyl]-amide as a white powder (230 mg),
m.p. : 156-158°C
mass spec m/z : 547 (M+1).

from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (300 mg) and 1H-pyrrole-2-carboxaldehyde (67 mg).

Example 3

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl)-piperazin-1-yl)-phenyl]-amide as a yellow powder (70 mg),

m.p. : 150-152°C

mass spec m/z : 614 (M+1)

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (250 mg) and 3-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzaldehyde (107 mg).

Example 4

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl)-piperazin-1-yl)-phenyl]-amide as a powder (70 mg),

m.p. : 172-174°C

mass spec m/z : 640 (M+1).

from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (300 mg) and 3-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzaldehyde (132 mg).

Example 5

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-thiophen-2-ylmethyl-piperazin-1-yl)-phenyl]-amide as a white powder (130 mg),

m.p. : 150-151°C

mass spec m/z : 538 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and thiophene-2-carboxaldehyde (123 mg).

Example 6

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-propyl-piperazin-1-yl)-phenyl]-amide as a pale yellow solid (86 mg),

m.p. : 176°C

mass spec m/z : 510 (M+1).

from 6-isopropyl-4'-trifluoromethyl -biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (267 mg) and propionaldehyde (40 mg).

Example 7

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-isobutyl-piperazin-1-yl)-phenyl]-amide as a white solid (190 mg),

m.p. : 135-137°C

mass spec m/z : 498 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (330 mg) and 2-methyl-propionaldehyde (64 mg).

Example 8

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-furan-2-ylmethyl-piperazin-1-yl)-phenyl]-amide as a white powder (320 mg),

m.p. : 136-138°C

mass spec m/z : 522 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and furan-2-carboxaldehyde (105 mg).

Example 9

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-thiazol-2-ylmethyl-piperazin-1-yl)-phenyl]-amide as a beige solid (310 mg),

m.p. : 160-162°C

mass spec m/z : 539 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and thiazole-2-carboxaldehyde (124 mg).

Example 10

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(5-bromo-furan-2-ylmethyl)-piperazin-1-yl)-phenyl]-amide as a yellow powder (400 mg),

m.p. : 138-140°C

mass spec m/z : 601 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 5-bromo-furan-2-carboxaldehyde (192 mg).

Example 11

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(5-bromo-thien-2-ylmethyl)-piperazin-1-yl)-phenyl]-amide as a powder (170 mg),
m.p. : 158-160°C
mass spec m/z : 617 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 5-bromo-thiophene-2-carboxaldehyde (210 mg).

Example 12
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-((2-methyl-thiazol-4-yl)methyl)-piperazin-1-yl)-phenyl]-amide as a white powder (240 mg),
m.p. : 110-112°C
mass spec m/z : 553 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 2-methyl-thiazole-4-carboxaldehyde (139 mg).

Example 13
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(1H-pyrazol-3-ylmethyl)-piperazin-1-yl]-phenyl}-amide as a white powder (100 mg),
m.p. : 166-168°C
mass spec m/z : 522 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 1H-pyrazole-3-carboxaldehyde (105 mg).

Example 14
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-thiophen-3-ylmethyl-piperazin-1-yl)-phenyl]-amide as a white powder (220 mg),
m.p. :142-144°C
mass spec m/z : 538 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and thiophene-3-carboxaldehyde (123 mg).

Example 15
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(3-methyl-1H-pyrrol-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide as a brown powder (30 mg),
m.p. :104-106°C

mass spec m/z : 535 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (440 mg) and 3-methyl-1H-pyrrole-2-carboxaldehyde (110 mg).

Example 16
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(1-methyl-1H-pyrrol-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide as a white powder (130 mg),
m.p. :166-168°C
mass spec m/z : 535 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (440 mg) and 1-methyl-1H-pyrrole-2-carboxaldehyde (120 mg).

Example 17
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(5-cyano-furan-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide as a white powder (230 mg),
m.p. :140-142°C
mass spec m/z : 547 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (440 mg) and 5-formyl-furan-2-carbonitrile (117 mg).

Example 18
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid {4-[4-(5-cyano-furan-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide as a white powder (295 mg),
m.p. :144°C
mass spec m/z : 573 (M+1).
from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (350 mg) and 5-formyl-furan-2-carbonitrile (108 mg).

Example 19
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-propyl-piperazin-1-yl)-phenyl]-amide
To a stirred solution of 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and cesium carbonate (390 mg) in acetone (30 mL) was added 1-bromopropane (148 mg). The mixture was heated under reflux overnight and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried over

Na_2SO_4 and evaporated under reduced pressure. The solid residue was crystallized from diisopropyl ether to give the title compound as a white powder (240 mg).
m.p.: 130-131°C
mass spec m/z : 484 (M+1).

Similarly prepared were :

Example 20
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-isopropyl-piperazin-1-yl)-phenyl]-amide as a white powder (270 mg),
m.p.: 138-140°C
mass spec m/z : 484 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 2-bromo-propane (148 mg).

Example 21
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-allyl-piperazin-1-yl)-phenyl]-amide as a white powder (60 mg),
m.p. : 148-150°C
mass spec m/z : 482 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and allyl-bromide (145 mg).

Example 22
6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-allyl-piperazin-1-yl)-phenyl]-amide as a white powder (175 mg),
m.p. : 186°C
mass spec m/z : 508 (M+1).
from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (350 mg) and allyl-bromide (108 mg).

Example 23
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(3-methyl-but-2-enyl)-piperazin-1-yl]-phenyl}-amide as a white powder (120 mg),
m.p. : 108-110°C
mass spec m/z : 510 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 1-bromo-3-methyl-but-2-ene (164 mg).

Example 24

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-cyclopropylmethyl-piperazin-1-yl)-phenyl]-amide as a white powder (20 mg),

m.p. : 124-126°C

mass spec m/z : 496 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and bromomethyl-cyclopropane (148 mg).

Example 25

4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-phenyl}-amide as a white powder (190 mg),

m.p. : 144-146°C

mass spec m/z : 500 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 1-bromo-2-methoxy-ethane (152 mg).

Example 26

4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(3,3,3-trifluoro-propyl)-piperazin-1-yl]-phenyl}-amide as a white powder (80 mg),

m.p. : 154-156°C

mass spec m/z : 538 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 3-bromo-1,1,1-trifluoro-propane (195 mg).

Example 27

4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-phenyl}-amide as a pale yellow solid (90 mg),

m.p. : 162-164°C

mass spec m/z : 486 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 2-bromo-ethanol (138 mg).

Example 28

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-carbamoylmethyl-piperazin-1-yl)-phenyl]-amide as a white powder (140 mg),

m.p. : 206-208°C

mass spec m/z : 499 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (300 mg) and 2-bromo-acetamide (103 mg).

Example 29

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-carbamoylmethyl-piperazin-1-yl)-phenyl] amide as a white powder (180 mg),

m.p. : 180-182°C

mass spec m/z : 525 (M+1).

from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (300 mg) and 2-bromo-acetamide (98 mg).

Example 30

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide as a white powder (90 mg),

m.p. : 140-141°C

mass spec m/z : 456 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and methyl iodide (171 mg).

Example 31

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(cyano-methyl)-piperazin-1-yl)-phenyl]-amide as a beige solid (165 mg),

m.p. : 220-221°C

mass spec m/z : 481 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and chloro-acetonitrile (91 mg).

Example 32

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-ethoxycarbonylmethyl-piperazin-1-yl)-phenyl]-amide as a beige solid (200 mg),

m.p. : 166-168°C
mass spec m/z : 528 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and bromo-acetic acid ethyl ester (200 mg).

Example 33
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(pyridin-2-ylmethyl)-piperazin-1-yl)-phenyl]-amide as a pale yellow solid (330 mg),
m.p. :160-161°C
mass spec m/z : 533 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 2-chloromethyl-pyridine hydrochloride (197 mg).

Example 34
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(pyridin-3-ylmethyl)-piperazin-1-yl)-phenyl]-amide as a pale yellow solid (270 mg),
m.p. : 196-198°C
mass spec m/z : 533 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 3-chloromethyl-pyridine hydrochloride (197 mg).

Example 35
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(pyridin-4-ylmethyl)-piperazin-1-yl)-phenyl]-amide as a pale yellow solid (150 mg),
m.p. : 132-134°C
mass spec m/z : 533 (M+1).
from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 4-chloromethyl-pyridine hydrochloride (197 mg).

Example 36
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-fluorobenzyl)-piperazin-1-yl)-phenyl]-amide as a white powder (220 mg),
m.p. : 124-125°C
mass spec m/z : 550 (M+1).

from 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) and 3-fluoro-benzyl bromide (230 mg).

Example 37

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide

To a stirred solution of 4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenylamine (150 mg), 4',6-diisopropyl-biphenyl-2-carboxylic acid (141 mg), HOBt (87 mg), and Et_3N (64 mg) in CH_2Cl_2 (10 mL) was added at room temperature EDCI (124 mg) and the mixture was stirred at room temperature for 16 hours. The organic solution was then washed with water, with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After filtration and evaporation of the filtrate, the oily residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (98/2) and crystallized from MeOH to give the title compound (140 mg) as white crystals.

m.p. : 156-158°C

mass spec m/z :557 (M+1).

Similarly prepared were :

Example 38

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide as a white solid (90 mg),

m.p. : 100°C

mass spec m/z : 583 (M+1).

from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (154 mg) and 4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenylamine (150 mg).

Example 39

6-Fluoro-4'-isopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide as a white solid (160 mg),

m.p. : 163-165°C

mass spec m/z : 533 (M+1).

from 6-fluoro-4'-isopropyl-biphenyl-2-carboxylic acid (130 mg) and 4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenylamine (150 mg).

Example 40

6-Fluoro-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide as a white solid (200 mg),

m.p. : 201-203°C

mass spec m/z : 559 (M+1).

from 6-fluoro-4'-trifluoromethyl-biphenyl-2-carboxylic acid (142 mg) and 4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenylamine (150 mg).

Example 41

6-Chloro-4'-isopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide as a white solid (400 mg),

m.p. :199-201°C

mass spec m/z : 550 (M+1).

from 6-chloro-4'-isopropyl-biphenyl-2-carboxylic acid (274 mg) and 4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenylamine (292 mg).

Example 42

4'-Isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide as a white solid (190 mg),

m.p. :145-147°C

mass spec m/z : 583 (M+1).

from 4'-isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid (154 mg) and 4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenylamine (150 mg).

Example 43

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide as a white solid (130 mg),

m.p. : 168°C

mass spec m/z : 482 (M+1).

from 6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid (268 mg) and 4-(4-methyl-piperazin-1-yl)-phenylamine (200 mg).

Example 44

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide

To a stirred solution of 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) in CH_2Cl_2 (15 mL) containing Et_3N (111 mg) was added dropwise acetyl bromide (135 mg) and the mixture was stirred at room temperature for 16 hours. The solution was then washed with water, with brine, dried over Na_2SO_4, filtered and evaporated. The residue was then purified by flash chromatography eluting with CH_2Cl_2/MeOH (95/5) and crystallized from pentane to give the title compound (300 mg) as a white powder.
m.p. : 222-224°C.
mass spec m/z : 484 (M+1).

Example 45

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide

To a solution of 4',6-diisopropyl-biphenyl-2-carboxylic acid (4-piperazin-1-yl-phenyl)-amide (441 mg) in CH_2Cl_2 (10 mL) containing Et_3N (111 mg) was added methanesulfonyl chloride (126 mg) and the mixture was stirred at room temperature for 16 hours. The solution was washed with water, with brine and dried over Na_2SO_4, filtered and evaporated. The residue was then purified by flash chromatography eluting with CH_2Cl_2/MeOH (95/5) and crystallized from pentane to give the title compound (370 mg) as a white powder.
m.p. : 260-262°C.
mass spec m/z : 520 (M+1).

Example 46

4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-hydroxycarbonylmethyl-piperazin-1-yl)-phenyl]-amide

To a solution of 4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-ethoxycarbonyl methyl-piperazin-1-yl)-phenyl]-amide (259 mg) in EtOH (20 mL) was added a 1N solution of NaOH (1 mL) and the mixture was heated under reflux for 3 hours. The solution was then cooled and neutralized with a 1N solution of HCl (1 mL) and the precipitate was filtered and dried to give the title compound (180 mg) as a powder.
m.p. : 122°C.

Biological Data

Examples of the invention were tested *in vitro*, using the biological assays described below. All of the compounds had an IC_{50} value of 0.2 nM or below in the MTP assay.

Biological Assay

ApoB-100 Assay

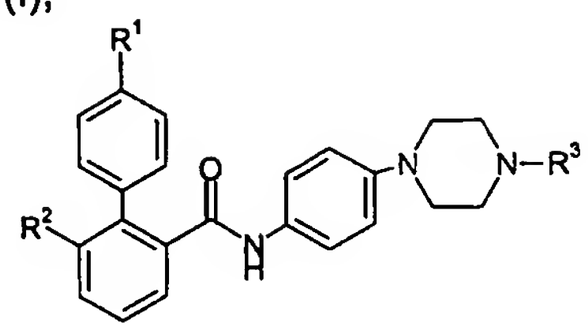
Primary human hepatocytes were seeded at 50 000 cells/well in 96 well plates. After an overnight adhesion phase, cells were incubated with compounds for 8 hours in RPMI medium containing 1% FCS, 4 µg/ml insulin, 100 nM dexamethasone and 50 µCi/ml ^{35}S-methionine. Compounds were dissolved in DMSO and tested onto cells from 1 µM to 1.6 nM. Production of radiolabeled apoB-100 and apoA-1 (used as a selectivity control) was quantified by analysis of supernatants using SDS PAGE and exposure of gels onto PhosphorImager screens. Inhibition of apoB-100 and apoA-1 secretion by compounds was calculated taking untreated cells as controls, and IC_{50} of each compound was determined on both apoproteins.

MTP Assay

The human MTP activity assay was established using SPA technology. Donor liposomes were prepared with 3H-triolein and phosphatidylcholine, while acceptor liposomes contained biotinylated phosphatidylethanolamine and phosphatidylcholine. The MTP-mediated 3H-triolein transfer onto acceptor liposomes was allowed by a 25 min inoubation at 37°C, and quantified by the addition of streptavidin-SPA beads.

Claims

1. A compound of formula (I);



(I)

wherein

R^1 represents isopropyl or trifluoromethyl,

R^2 represents isopropyl, chloro, fluoro or trifluoromethyl,

R^3 represents C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{1-4}alkylsulfonyl, C_{1-4}acyl or $-CH_2-R^4$;

R^4 represents:

(i) phenyl, optionally substituted by cyano, fluoro or an optionally substituted 5-membered heteroaromatic group, where optional substitution is effected by C_{1-4}alkyl or C_{1-3}perfluoroalkyl,

(ii) a 5 or 6 membered heteroaromatic group, optionally substituted by halogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy or C_{3-7}cycloalkyl,

(iii) C_{3-7}cycloalkyl,

(iv) cyano,

(v) hydroxycarbonyl, C_{1-4}alkoxycarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl, C_{1-4}dialkylaminocarbonyl,

(vi) C_{1-4}alkoxyC_{1-4}alkyl, hydroxyC_{1-4}alkyl or

(vii) trifluoromethylC_{1-4}alkyl;

or a physiologically acceptable salt, solvate or derivative thereof.

2. A compound of formula (I) according to claim 1, wherein R^1 represents isopropyl, or a physiologically acceptable salt, solvate or derivative thereof.

3. A compound of formula (I) according to claim 1 or claim 2, wherein R^2 represents isopropyl or trifluoromethyl, or a physiologically acceptable salt, solvate or derivative thereof.

4. A compound of formula (I) according to any one of claims 1 to 3, wherein R^4 represents:

viii) phenyl, optionally substituted by cyano, fluoro or an optionally substituted 5-membered heteroaromatic group;

ix) a 5- or 6- membered heteroaromatic group; optionally substituted by halogen, cyano or C_{1-4}alkyl;

x) C_{3-7}cycloalkyl,

xi) cyano,

xii) C_{1-4}alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl,

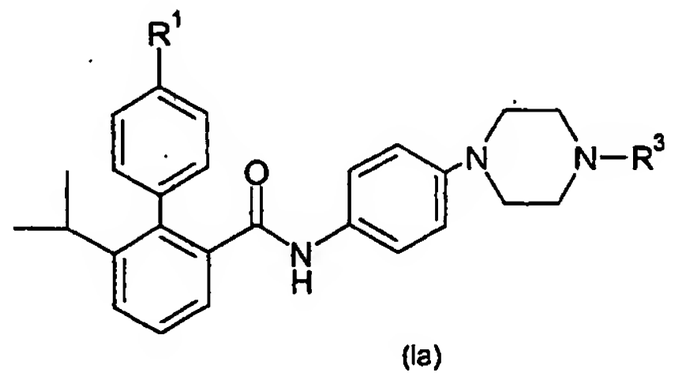
xiii) C_{1-4}alkoxymethyl, hydroxyC_{1-4}alkyl, or

xiv) trifluoromethylC_{1-4}alkyl;

or a physiologically acceptable salt, solvate or derivative thereof.

5. A compound of formula (I) according to any one of claims 1 to 4, wherein R^3 represents methyl, propyl, isopropyl, isobutyl, propen-2-yl, methoxymethyl, hydroxyethyl, phenylmethyl substituted by 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or an optionally substituted pyrrolylmethyl, thienylmethyl or furanylmethyl group, where optional substitution is effected by methyl or cyano; or a physiologically acceptable salt, solvate or derivative thereof.

6. A compound of formula (I) according to any one of claims 1 to 5, wherein the compound of formula (I) is represented by a formula (Ia)



(Ia)

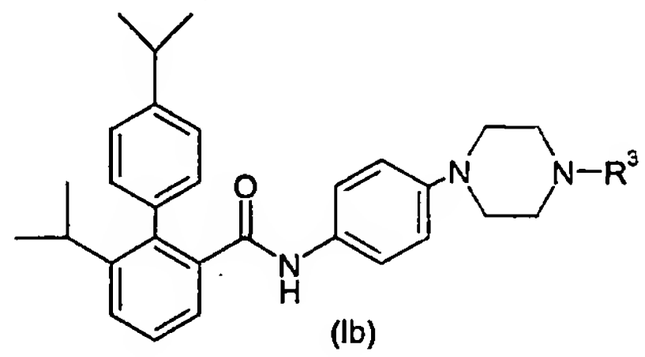
wherein

R^1 represents isopropyl or trifluoromethyl,

R^3 represents C_{1-4}alkyl, C_{2-6}alkenyl, acetyl, methylsulfonyl or $-CH_2-R^4$;

R^4 represents aminocarbonyl, cyano, ethoxycarbonyl, hydroxycarbonyl, C_{1-4}alkoxymethyl, trifluoromethylC_{1-4}alkyl, C_{3-7}cycloalkyl, phenyl substituted by 3-fluoro, 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or a 5- or 6- membered heteroaromatic group, optionally substituted by bromo, methyl or cyano; or a physiologically acceptable salt, solvate or derivative thereof.

7. A compound of formula (I) according to any one of claims 1 to 5 wherein the compound of formula (I) is represented by a formula (Ib)



(Ib)

wherein

R^3 represents C_{1-4}alkyl ,C_{2-6}alkenyl or $-CH_2-R^4$; and

R^4 represents phenyl substituted by 3-cyano or 3-(3-methyl-[1,2,4]oxadiazol-5-yl), or a 5- membered heteroaromatic goup selected from pyrrolyl, thienyl, furanyl, thiazolyl and pyrazolyl, optionally substituted by halogen, methyl or cyano; or a physiologically acceptable salt, solvate or derivative thereof.

8. A compound of formula (I) according to claim 1, selected from the group comprising :

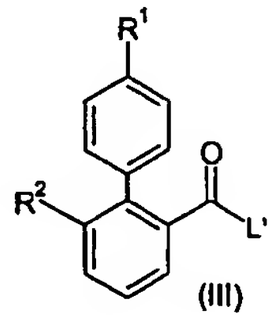
4'-isopropyl-6-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;

6-isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;

6-Isopropyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid {4-[4-(5-cyano-furan-2-ylmethyl)-piperazin-1-yl]-phenyl}-amide;

4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(3-cyano-benzyl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((thien-3-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((furan-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-((5-cyano-furan-2-yl)methyl)-piperazin-1-yl)phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-propyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-isopropyl-piperazin-1-yl)-phenyl]-amide;
4',6-Diisopropyl-biphenyl-2-carboxylic acid [4-(4-isobutyl-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(propen-2-yl)-piperazin-1-yl)-phenyl]-amide;
4',6-diisopropyl-biphenyl-2-carboxylic acid [4-(4-(2-methoxyethyl)-piperazin-1-yl)-phenyl]-amide;
4',6-Diisopropyl-biphenyl-2-carboxylic acid {4-[4-(2-hydroxyethyl)-piperazin-1-yl]-phenyl}-amide;
or a physiologically acceptable salt, solvate or derivative thereof.

9. An intermediate of formula (III)



(III)

wherein L' is OH, R^1 is isopropyl or trifluoromethyl and R^2 is chloro, fluoro, isopropyl or trifluoromethyl.

10. A compound of formula (I) or a physiologically acceptable salt or solvate thereof according to any one of claims 1 to 8 for use in therapy.

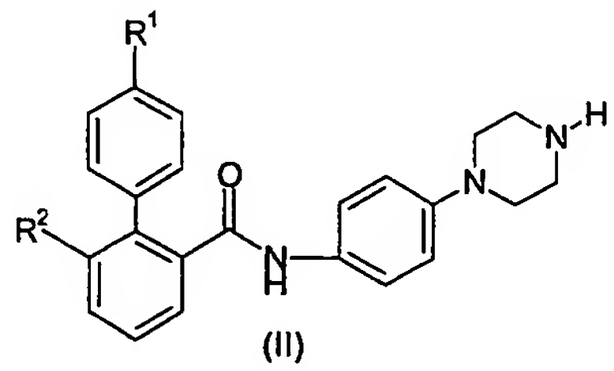
11. Use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof according to any one of claims 1 to 8 in the preparation of a medicament for use in the treatment of conditions ameliorated by an apoB-100 and/or MTP inhibitor.

12. Use of a compound of formula (I) according to claim 7, or a physiologically acceptable salt or solvate thereof, for use in the preparation of a medicament for the treatment of atherosclerosis, pancreatitis, non-insulin dependant diabetes mellitus (NIDDM), coronary heart diseases and obesity.

13. A method of treating a mammal comprising administration of an effective amount of a compound of formula (I) according to any one of claims 1 to 8, or a physiologically acceptable salt or solvate thereof in the treatment of conditions ameliorated by an apoB-100 and/or MTP inhibitor.

14. A pharmaceutical composition comprising at least one compound of formula (I) according to any of claims 1 to 8, or a physiologically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers or excipients.

15. A process for the preparation of a compound of formula (I) or a physiologically acceptable salt or solvate thereof comprising reacting a compound of formula (II) with a compound of formula R^3-L



(II)

where L represents a suitable halide leaving group under standard displacement conditions, or L may additonally represent a hydroxy group, the reaction being effected under standard acid and amine coupling conditions.

INTERNATIONAL SEARCH REPORT

b onal Application No
PCT/EP 02/13592

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/32 C07D271/06 C07D333/20 C07D295/12 C07D277/28
C07D231/12 C07D295/14 C07D295/18 C07D295/22 A61K31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 32582 A (GLAXO GROUP LTD) 8 June 2000 (2000-06-08) page 1, line 17 - page 12, line 16; page 18, line 22 - page 19, line 16; page 23, lines 4-21; claims 1-20, 23-27 & PCT Application PCT/EP99/09320 cited in the application	1-15
A	WO 96 40640 A (PFIZER INC) 19 December 1996 (1996-12-19) cited in the application page 1, line 27 - page 6, line 20	1,8-14
P,A	WO 01 97810 A (GLAXO GROUP LTD) 27 December 2001 (2001-12-27) page 1, line 24 - page 12, line 22; page 18, line 34 - page 19, line 4; page 23, lines 1-18; claims	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2003	28/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/EP 02/13592

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 92241 A (GLAXO GROUP LTD) 6 December 2001 (2001-12-06) page 9, formula III; pages 14-16, intermediates 8-14	9
P,X	G.M. KSANDER ET AL: J. MED. CHEM., vol. 44, no. 26, 20 December 2001 (2001-12-20), pages 4677-4687, XP001118264 page 4684, column 2, compound 8eR in combination with page 4678, scheme 1, steps (b)-(c)	9

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 02/13592

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/13592

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